UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/657,006	09/05/2003	Christine Dingivan	10271-116-999	3565

20583 7590 10/24/2006

JONES DAY
222 EAST 41ST ST
NEW YORK, NY 10017

EXAMINER	
SKELDING, ZACHARY S	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 10/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/657,006	DINGIVAN ET AL.	
	Examiner	Art Unit	
	Zachary Skelding	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-44* is/are pending in the application.

4a) Of the above claim(s) *2,16,18-22 and 33-43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-15, 17, 23-32 and 44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *August 23, 2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election in the reply filed on July 11, 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

   Claims 1-44 are pending.

2. Upon further consideration, the prior art search has been extended to include the disease species "anaplastic large cell lymphoma" recited, for example, in claim 15.

   Claims 1, 3-15, 17, 23-32 and 44 are under examination as they read on a method for treating cancer comprising administering an anti-CD2 antibody, wherein the elected species are as follows:
   - the anti-CD2 antibody is **"MEDI-507"** and **"an anti-CD2 antibody with the proviso that said antibody is NOT MEDI-507"** ***but it has the same properties as MEDI-507***;
   - the type of cancer is **"peripheral T-cell lymphoma" or "anaplastic large cell lymphoma"**;
   - the type of experimental therapy is **"aggressive combination chemotherapy"**;
   - the therapeutic agent or drug conjugated to antibody is **"auristatin PHE"; and**
   - the cancer therapeutic is **"cyclophosphamide"**.

   Claims 2, 16, 18-22 and 33-43 have been withdrawn from further consideration by the Examiner, under 37 C.F.R. § 1.142(b), as being directed to a non-elected invention.

3. The instant application appears to be in sequence compliance for patent applications containing nucleotide sequence and/or amino acid sequence disclosures.

4. The instant claims appear to have be entitled to the benefit of priority of USSN 60/409,024.

5. Applicant's information disclosure statement, filed August 23, 2006 has been considered.

6. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected.

   Each letter of trademarked terms should be capitalized wherever it appears and each trademarked term should be accompanied by the generic terminology, e.g., ™ or ®. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

   The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware in the specification.

7. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

8. **Claims 1, 3, 8, 9 and 11, and dependent claims thereof, are rejected under 35 U.S.C. 112, second paragraph**, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

   The instant claims are indefinite in the recitation of **"MEDI-507"** and **"LO-CD2a/BTI-322"**, as the sole means of identifying these antibodies because these terms are merely laboratory designations which do not clearly define these antibodies, since different laboratories may use the same designations to define completely distinct biological materials.

   Amending the claims to recite the appropriate ATCC Accession Numbers would obviate this rejection.

   Applicant is reminded that any amendment to the claims must point to a basis in the specification so as not to add any new matter. See MPEP 714.02 and 2163.06.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

   The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. **Claims 1, 3-15, 17, 23-32 and 44 are rejected under 35 U.S.C. 112, first paragraph,** as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

    A. It is apparent that the **"MEDI-507"** and **"LO-CD2a/BTI-322"** antibodies are required to practice the instant claims. As required elements, they must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If they are not so obtainable or available, the enablement requirements of 35 USC 112, first paragraph, may be satisfied by a deposit of the pertinent cell lines/hybridomas which produce these antibodies. See 37 CFR 1.801-1.809.

    In addition to the conditions under the Budapest Treaty, applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If the deposit is made after the effective filing date of an application for patent, applicant should promptly submit a verified statement, ***from a person in a position to corroborate the fact***, that the biological material which is deposited is the same as the biological material specifically identified in the application as filed, i.e., is the same as the "MEDI-507" and "LO-CD2a/BTI-322" antibodies disclosed in the instant specification. This statement should be verified except if the person is an attorney or agent registered to practice before the Office, in which case the statement need not be verified. See MPEP 1.804(b).

This rejection will be maintained until such time the applicant clarifies for the record the public availability of "MEDI-507" and "LO-CD2a/BTI-322" with respect to the requirements for the deposit of biological materials under 35 U.S.C. § 112, 1st paragraph, see MPEP 2400.

B. Claims 1-7 recite a method for treating or ameliorating ***any*** cancer comprising administering an anti-CD2 antibody. However, as stated in the instant specification on page 6, section 2.4, CD2 is a T-cell surface antigen "expressed on >95% of thymocytes and virtually all peripheral T lymphocytes." Thus, one of ordinary skill in the art would not know how to use an anti-CD2 antibody to treat ***any*** cancer, including those which do not have T-cell involvement, for example, pancreatic carcinoma.

Thus, undue experimentation would be required to produce the claimed invention commensurate with the scope of the claims from the written disclosure alone. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to use an anti-CD2 antibody to treat ***any*** cancer, including those which do not have T-cell involvement, for example, pancreatic carcinoma.

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. **Claims 1, 6, 7, 26-31, 33-37, 39, 40, 62, 63, 66 and 69 are rejected under 35 U.S.C. 103(a)** as being unpatentable over **Bazin et al.** (WO 99/03502)(cited on applicant's IDS of November 21, 2003) in view of **White et al.** (Journal of clinical pathology, (1989 Apr) Vol. 42, No. 4, pp. 403-8), **Lin et al.** (Medical and pediatric oncology, (1994) Vol. 23, No. 1, pp. 26-35), **Au et al.** (Curr Oncol Rep. 2002 Sep;4(5):434-42), **Neville et al.** (USSN 10/296,085), **Doronina et al.** (USSN 09/845,786), Wallner (U.S. Patent No. 6,162,432) and **Lin J et al.** (Cell Immunol. 1996 Feb 1;167(2):249-58)(see entire documents).

Bazin et al. teach a method for inhibiting proliferation of T cells in a human comprising administering a therapeutically effective amount such as of MEDI-507 or antigen-binding fragment thereof **OR** an antibody that immunospecifically binds to an epitope comprising amino acid residues 18, 55 or 59 of human CD2, with the proviso that said antibody is not MEDI-507 or LO-CD2a/BTI-322, for example an antibody that binds to the same epitope (or any part thereof) on human lymphocytes as the Lo-CD2a antibody (see entire document, in particular page 1, 1st paragraph and page 12, 5th paragraph to page 13, 1st paragraph).

It is noted that claim 44 recites administration of CD2 binding agent at a dose between 0.1-10 mg/kg/week, which given its broadest reasonable interpretation consistent with the instant specification, encompasses a unit of dose of 8-800 mg/week based on an average weight of 80 kg (176 lbs) for the average human subject having cancer.

Bazin teaches the *in vivo* immunodepletion of $CD2^+$ lymphocytes with LO-CD2a/BTI-322, or an antibody that binds the same epitope or any part thereof, in humans, for example via the administration of 70 mg antibody over the course of a week, or in non-human primates (see entire document, in particular page 38, 4th paragraph to page 39, 1st paragraph (human) and page 31, 5th paragraph to the paragraph bridging pages 36 and 37 and Figure 13 (non-human primates). Bazin also demonstrates the equivalent abilities of LO-CD2a/BTI-322 and MEDI-507 to immunodeplete $CD2^+$ lymphocytes in mice ((and page 89, 3rd paragraph to page 90).

Moreover, Bazin teaches that the LO-CD2a and MEDI-507 antibodies can be administered at an initial dose of at least 1 mg via intravenous infusion, and that higher or lower doses may be called for depending upon patient response.

The claimed invention differs from the reference teaching in the recitation of treating cancer, in particular the species **"peripheral T-cell lymphoma" or "anaplastic large cell lymphoma"**, the additional administration of a cancer therapeutic, in particular the species **"cyclophosphamide"** the use of an additional standard therapeutic regimen, in particular the species **"aggressive combination chemotherapy"**, conjugation of MEDI-507 to a therapeutic agent or drug, in particular the species **"auristatin PHE"** and in the recitation of wherein additional standard therapeutic regimen is administered **"prior to, concomitantly with, or subsequent to the administration of MEDI-507"**.

It is noted that the standard therapeutic regimen **"aggressive combination chemotherapy", given its broadest reasonable interpretation consistent with the instant specification,** will be interpreted as encompassing the combination of two or more chemotherapeutic agents using a treatment regimen, i.e., dose and scheduling, as directed by a physician of ordinary skill in the art.

White teaches that biopsies taken from ten of eleven patients with peripheral T cell lymphoma were positive for CD2 expression, and that all were positive for CD3 expression (see entire document, in particular Abstract and Introduction, page 403). White also teaches ten of eleven peripheral T cell lymphoma patients were treated with "combination chemotherapy", with one patient failing to respond and nine exhibiting only a partial response (see, in particular page 406, left column).

Lin teaches that biopsies taken from five of five patients with peripheral T cell lymphoma were positive for CD2 and CD3 expression (see entire document, in particular Abstract and Introduction, page 26). It is further noted that Lin also teaches the treatment of peripheral T cell lymphomas with "combination chemotherapy" regimens, such as CHOP (as known by one of ordinary skill in the art CHOP, is an acronym for **Cyclophosphamide**, Adriamycin, which has the brand name of Hydroxydoxorubicin, Vincristine, which goes by the brand name Onocovin, and the drug Prednisone)(see, in particular Discussion pages 33-34).

Au teaches that "the term **'peripheral T-cell lymphoma'** refers to malignant lymphoproliferation of T cells of post-thymic origin in differentiation (peripheral T cells)" and encompasses at least eight distinct disease entities, including **cutaneous T-cell lymphoma, mycosis fungoides, Sezany syndrome and anaplastic large cell lymphoma** (see, in particular Introduction, page 434).

For prior art examination purposes, the cancer species **"peripheral T-cell lymphoma", given its broadest reasonable interpretation consistent with the instant specification,** will be interpreted as encompassing the diseases taught by Au as described the preceding paragraph.

Au further teaches that "aggressive combination chemotherapy appears to be curative for certain entities", and that, "as in B-cell lymphomas, disease-specific T-cell monoclonal antibody-based therapy may represent a new treatment direction" (see, in particular, abstract and conclusion, pages 434 and 438, as well as Results pages 435-438 for descriptions of various forms of peripheral T-cell lymphomas and the combination chemotherapy regimens used in their treatment).

Wallner teaches a method of inhibiting T cell proliferation and activation, for example to treat cutaneous T cell lymphoma such as mycosis fungoides, comprising administering to a subject in need thereof a therapeutically effective amount of an anti-CD2 antibody, including the $T11_2$ anti-CD2 antibodies (see entire document, in particular column 1 through column 7, line 31). As is well known by one of ordinary skill in the art, $T11_2$ anti-CD2 antibodies are characterized by the fact that they do not inhibit the interaction between CD2 and LFA-3 (see, e.g., Richardson et al., Proc Natl Acad Sci U S A. 1988 Jul;85(14):5176-80, in particular Introduction page 5176).

Wallner further teaches that with regard to administration of a therapeutically effective amount of an anti-CD2 antibody, including an antibody that does not inhibit or interfere with the interaction between human CD2 and LFA-3, such as a $T11_2$ anti-CD2 antibody, it will be apparent to those of skill in the art that the effective amount of inhibitor will depend, *inter alia*, upon the administration **schedule**, the **unit dose** administered, **whether the inhibitor is administered in combination with other therapeutic agents**, the immune status and health of the patient, the therapeutic or prophylactic activity of the particular inhibitor administered and the serum half-life. Moreover, Wallner teaches that "unit doses should **be administered until an effect is observed**...[m]ore preferably, it is administered about one to three times per day for between about 3 and 7 days, or about one to three times per day for between about 3 and 7 days **on a monthly basis**. It will be recognized, however, that **lower or higher dosages and other administrations schedules may be employed**." Wallner also teaches concurrent or sequential administration of anti-CD2 antibody and additional therapeutic/prophylactic agents, including chemotherapeutic agents, and various routes of anti-CD2 antibody administration, including intravenously, subcutaneously, intramuscularly, orally, and by inhalation, i.e., intranasally (See, in particular, page column 15, line 60 to column 17, line 17).

Thus, according to the teaching of Wallner, the dosage and scheduling of administration of anti-CD2 antibody, including with respect to combination with other therapeutic agents, is an art recognized results-effective variables, i.e., variables that are recognized as important for therapeutic use of anti-CD2 antibody and which therefore can be optimized by routine experimentation. See M.P.E.P. § 2144.05 II.B. and *In re Antonie*, 559 F.2d 618, 195 USPQ 6 (CCPA 1977).

It is noted that while Wallner does not appear to explicitly teach the administration of MEDI-507 for six months as recited in claim 44, this claim is included in the instant rejection because Wallner recognizes the scheduling of antibody and therapeutic/prophylactic agent to be a results-effective variable and provides guidance and direction for their optimization by routine experimentation as described above. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955), and see M.P.E.P. § 2144.05 II.A.

Neville teaches the use of an anti-T-cell immunotoxin fusion protein, for example anti-CD3 antibody conjugated to an immunotoxin, to immunodeplete T cells to treat or ameliorate cancer, for example the peripheral T cell lymphomas cutaneous T-cell lymphoma, mycosis fungoides and Sezany syndrome (see entire document, in particular page 2, paragraph [0013], page 11, paragraph [0166], page 18, paragraph [0215] and pages 20-21, paragraph [0248]).

Neville further teaches the administration of cyclophosphamide in combination with anti-T-cell immunotoxin fusion protein (see entire document, in particular page 18, paragraph [0219]).

Doronina teaches how to conjugate an antibody which binds to a tumor associated cell surface protein and is internalized, such as anti-CD30 antibody, to a therapeutic agent or drug, such as auristatin PHE, which is a derivative of dolastatin 10 containing phenyl alanine and methyl ester substituents, via conjugation to the methyl ester substituent of auristatin PHE (see entire document, in particular, page 2, paragraphs [0024]-[0028]; page 23, paragraph [0302]; page 25, paragraphs [0322]-[0325].

Doronina further teaches that a particular anti-CD30-auristatin E conjugate has cytotoxic effects on a cell line derived from a peripheral T cell lymphoma, specifically $CD30^+$ anaplastic large cell lymphoma (see, in particular page 34, example 19 and Figure 13B).

Lin J teaches that anti-CD2 and anti-CD3 antibodies induce CD2 and CD3 internalization (see entire document, in particular Discussion, pages 255-257).

Given the combined teachings, one of ordinary skill in the art at the time the invention was made would have been motivated and would have **had a reasonable expectation of success of inhibiting proliferation of T cells in a human, for example in a human with a peripheral T-cell lymphoma or anaplastic large cell lymphoma**, comprising administering a therapeutically effective amount of MEDI-507 or antigen-binding fragment thereof OR an antibody that immunospecifically binds to an epitope comprising amino acid residues 18, 55 or 59 of human CD2, with the proviso that said antibody is not MEDI-507 or LO-CD2a/BTI-322, **for example an antibody that binds to the same epitope (or any part thereof) on human lymphocytes as the Lo-CD2a antibody as taught by Bazin** and further administering the cancer therapeutic cyclophosphamide or combination chemotherapy as taught by White and Lin.

One of ordinary skill in the art would have been motivated to use the anti-CD2 antibodies of Bazin to treat peripheral T-cell disorders because Bazin teaches that the anti-CD2 antibodies effectively deplete T-cells, and White and Lin teach that CD2 is expressed in the majority of tumor samples obtained from individuals with peripheral T-cell disorders, and they teach these disorders respond poorly to treatment with combination chemotherapy alone.

Moreover, equipped with the teachings of Wallner, one of ordinary skill in the art would know to vary the scheduling and dosage of anti-CD2 antibody/additional cancer therapies, such as the chemotherapeutic agent cyclophosphamide, and no more than routine experimentation would be required to arrive at an optimized results effective dose schedule of 0.1 to 10 mg/kg/week for 6 months as recited in claim 44.

Lastly, given the strategy of preparing T-cell specific antibody-toxin conjugates that are internalized upon binding their target, such as anti-CD3 and anti-CD30 antibodies conjugated to an immunotoxin or auristatin-PHE, to treat T-cell lymphoproliferative conditions, such as the peripheral T cell lymphomas "cutaneous T-cell lymphoma", "mycosis fungoides", "Sezany syndrome" and "$CD30^+$ anaplastic large cell lymphoma", as taught by Neville, Doronina and Lin J, and further given the teachings of White and Lin that CD3 and CD2 are expressed on, or nearly all, biopsies harvested from patients with peripheral T cell lymphomas, one of ordinary skill in the art would have been motivated to make an antibody-toxin conjugate using another well known marker of peripheral T cell lymphoma, such as an anti-CD2 antibody auristatin-PHE conjugate, and to use said conjugate to treat peripheral T cell lymphoma.

Also, it was prima facie obvious to combine two compositions each of which is taught by prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose; idea of combining them flows logically from their having been individually taught in prior art. In re Kerkhoven, 205 USPQ 1069, CCPA 1980. See MPEP 2144.06.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention.

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary Skelding whose telephone number is 571-272-9033. The examiner can normally be reached on Monday - Friday 8:00 a.m. - 5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Zachary Skelding, Ph.D.
Patent Examiner
September 25, 2006

PHILLIP GAMBEL, PH.D. J.D.
PRIMARY EXAMINER
TC 1600
9/19/06